REMARKS

1. Election/Restriction (pp. 1-2)

We are in agreement with the Examiner that the dependent process claims should be rejoined once a product claim is deemed allowable, and we merely remind the Examiner to take this into account.

2. Objections (OA §§7-14)

The objected-to claims, which have not been cancelled, have been amended in accordance with the examiner's recommendations.

3. Claims

Claims 12-19 and 70-89 were examined. Claim 12 has been amended to be directed to an isolated polypeptide which

(a) comprises SEQ ID NO:2;
(b) consists of residues 234-1791 of SEQ ID NO:2;
(c) differs from the polypeptide of (b) solely by deletion of 1-10 residues from the amino terminal of (b) and/or deletion of 1-10 residues from the carboxy terminal of (b);
(d) differs from (b) solely by addition of 1-10 residues to the amino terminal or carboxy terminal of (b); or
(e) is at least 97% identical to a polypeptide of (a), (b), (c), or (d),

and which satisfies at least one of original functional limitations (i)-(iii).

SEQ ID NO:2 corresponds to "full length" PAPP-A2, or, more accurately, the precursor of mature PAPP-A2. See P4, L22-23; P5, L25-27; P7, L7-8. Basis for clause (a) appears at, e.g., P14, L9 and 17-22, and in original claim 12 ("...comprising...SEQ ID NO:2...).

The mature PAPP-A2 is residues 234-1791 of SEQ ID NO:2, which is the subject of clause (b). Basis for (b) exists in

e.g., original claim 13 and P43, L21-23.

Clause (c) contemplates truncation of up to 10 residues from either or both termini of mature PAPP-A2. Basis exists at P6, L34-P7, L2; P36, L33-P37, L3, P43, L21-23 and, most particularly, at P43, L33-P44, L3.

Clause (d) contemplates an "extension" of the mature sequence. Basis exists at P42, L21-24; P44, L5-9.

Finally, clause (e) contemplates introduction of a small number of amino acid substitutions into the polypeptides of (a)-(d). Clause (e) requires retention of at least 97% identity with at least one of polypeptides (a)-(d). Basis for 97% identity appears at P35, L17 and P38, L26-27.

New claim 90 is directed to

An isolated polypeptide which is

(1) a polypeptide consisting of an amino acid sequence which is identical to residues 234-1791 of SEQ ID NO:2, or a fragment, at least 6 amino acids in length, of mature PAPP-A2 (residues 234-1791 of SEQ ID NO:2) where said fragment

i) has a proteolytic activity specific at least for Insulin Like Growth Factor Binding Protein 5 (IGFBP-5); and/or

ii) is recognized by an antibody, or a binding fragment thereof, which recognizes a polypeptide having the amino acid sequence as shown in SEQ ID NO:2; and/or

iii) competes with a polypeptide having the amino acid sequence as shown in SEQ ID NO:2 for binding to a cell surface receptor with an affinity for said polypeptide

or

(2) a polypeptide which consists of a fusion of the polypeptide of (1) with an immunogenic carrier

protein, or with a tag which may be used to facilitate the detection or purification of the fusion, with the proviso that said fusion of (2) is not a pregnancy-associated plasma protein.

Clause (1) of claim 90 is based on original claim 12, which recited active fragments of SEQ ID NO:2 and P34, L23-P35, L3. Basis for 7 a.a. fragments exists at P7, L13-16. Such a fragment is sufficiently long to preserve a linear epitope of PAPP-A2, per activity (ii).

Clause (2) is based as the disclosure of fusion proteins, e.g., conjugates of PAPP-A2 fragments "to a carrier protein such as keyhole limpet hemocyanin". (P7, L19), or to an expression tag such as GST, c-myc or histidine (P14, L17-22). See also P15, L29-P16, L10; P17, L27-28. The proviso is used so that the claim cannot possibly read inadvertently on PAPP-A, PAPP-E, etc.

Claim 91 is specific to the fragment of 90(1). Claim 92 is based on P7, L13-16. Claim 93 is based on P35, L11. Claim 94 is based on P26, L20-P27, L2, and requires that the fragment comprise at least one of the following regions (numbering from SEQ ID NO:2):

Cys-403 to Cys-499
Cys-828 to Cys-881
Cys-1048 to Cys-1115
Cys-1390 to Cys-1396
Cys-1459 to Cys-1464
Cys-1521 to Cys-1525
Cys-1590 to Cys-1595
Cys-1646 to Cys-1653
Cys-1729 to Cys-1733.

Claim 95 is based on P52, L3-10 and P57, L17-22. Referring to Fig. 3, it can be seen that the first LNR1 begins at prepro PAPP-A2 586 and the last LNR1 ends at prepro PAPP-A2 ends at 1758. Referring to SEQ ID NO:2, the first Cys of mature PAPP-A2

(234-1791) is at 312 and the last Cys is at 1782. Thus, claim 95 is effectively directed to fragments of mature PAPP-A2 comprising amino acids 312-1782 of SEQ ID NO:2.

Claim 96 is based on P37, L18.

New claims 97-99 are based on P44, L16-21.

4. Prior Art Issues (OA §25, 26)

4.1. Claims 12-13, 18-19, 71-76, 78-84, 88-89 stand rejected as anticipated by Farr, et al. (2000).

Farr disclosed the 1624 a.a. PAPP-E polypeptide, which, according to the examiner, is 99.8% identical to amino acids 168-1791 of applicant's 1791 a.a. PAPP-A2 polypeptide (SEQ ID NO:2).

Farr's polypeptide plainly lacks amino acids 1-167 of SEQ ID NO:2, and therefore cannot anticipate amended 12 (a). Clauses (b) and (c) collectively cover fragments of SEQ ID NO:2 such that the N-terminal corresponds to any of AAs 224-234 of SEQ ID NO:2, and the (terminal to any of AAs 1781-1791 of SEQ ID NO:2. Farr's substantially larger polypeptide does not anticipate any of (b)-(c), which all use the closed claim term "consists of".

Clause (d) allows for up to 10 a.a. extension of mature PAPP-A2. Even the species corresponding to residues 224-1791 of SEQ ID NO:2 is not anticipated by Farr.

Finally, clause (e) allows for substitution mutants which remain at least 97% identical to at least one of (a)-(d).

Farr's polypeptide is 1624 a.a. long, and had two internal mismatches with SEQ ID NO:2. That yields an identity with full-length PAPP-A2 (polypeptide (a)) of 1622/1791, or just 90.6756%.

Now consider mature PAPP-A@ (234-1791 of SEQ ID NO:2). It is 1558 a.a. long; Farr would have an overhang of 1624-1558= 66 AAs +2 internal mismatches, so 68 mismatches on a base 1558. Farr is thus 95.63543% identical to polypeptide (b), which is still less than 97%.

Clause (c) covers truncated mature PAPP-A2. Truncation creates additional mismatches.

Clause (d) allows addition of 10 a.a. to the N-terminal of

mature PAPP-A2. Maximum identity to Farr's polypeptide is obtained if the addition is of residues 224-233 of SEQ ID NO:2. In this instance, there are 58 mismatches on a base of 1568, and thus a percentage identity of 96.30102%. That again is less than 97%.

It follows of Farr et al. does not anticipate claim 12 as amended.

Turning to new claim 90, clause (1) is directed to fragments of mature PAPP-A2, which is already smaller than PAPP-E. Clause (2) is directed to fusions, but the proviso ensures that the "fusion" does not read on PAPP-E.

4.2. Claims 12, 18-19, 71-75, 83 and 88-89 are rejected as anticipated by Hanning et al. (PIRS65464). The Examiner contended that the Hanning reference literally met the % identity limitation and inherently met the activity (epitope) limitation.

The overall alignment of Hanning AAs 80-1616 to the SEQ ID NO:2's AAs 249-1790 was just 39.7%.

The prior claim 12 allowed a 75% match with certain fragments of SEQ ID NO:2. The Examiner directed our attention to the Hanning et al. subsequences aligned with (1) AAs 818-835 (18 a.a. perfect match) and (2) AAs 1745-59 (15 a.a. sequence with 13 matches and 2 mismatches).

This rejection is moot as applied to amended claim 12. With respect to new claim 90, it is certainly possible that Hanning's PAPP-A (1627 a.a.) and our mature PAPP-A2 (1558 a.a.) or full-length PAPP-A2 (1791 a.a.) have one or more epitopes in common, despite the overall sequence identity of just 39.7%.

However, the Examiner has made no showing that it is likely, let alone certain, that one of the aforementioned two sequences comprises an epitope. For example, the Examiner has not analyzed the hydrophilicity of these sequences relative to the rest of the polypeptide.

The general rule concerning inherent anticipation is that the allegedly inherent feature must be certain to be present in view of the explicit features. See Ex parte Levy, 17 USPQ2d

1461, 1464 (BPAI 1990) ("inherent characteristic necessarily flows" from prior art teachings); Glaxo Inc. v. Novopharm Ltd., 29 USPQ2d 1126 (EDNC 1993), aff'd 34 USPQ2d 1565 (Fed. Cir. 1995) (allegedly inherent result must "invariably" happen); Electro Medical Systems, S.A. v. Cooper Life Sciences, Inc., 32 USPQ2d 1017, 1020 (Fed. Cir. 1994) (that a thing "may result" is insufficient); Motorola, Inc. v. Interdigital Technology Corp., 930 F. Supp. 952, 970 (D. Del. 1996); Marion Merrell Dow Inc. v. Geneva Pharmaceuticals, 33 USPQ2d 1673, 1677 (D. Col. 1994); Hughes Aircraft Co. v. United States, 8 USPQ2d 1580, 1583 (Claims Ct. 1988) (in anticipation-by-inherency cases, the element must "flow undeniably and irrefutably from the express disclosures"); Ethyl Molded Products Co. v. Betts Package, Inc., 9 USPQ2d 1001, 1032-3 (E.D. Ky. 1988) (doctrine requires "certainty"; "probabilities are not sufficient"); Phillips Petroleum Co. v. U.S. Steel Corp., 6 USPQ2d 1065, 1076-77 n. 12 (D. Del. 1987), aff'd 9 USPQ2d 1461 (Fed. Cir. 1989) ("anticipation...cannot be predicated on mere conjecture").

Claim 90 distinguishes Hanning because 90(1) must be a fragment, not merely comprise a fragment, and the fusion of 90(2) cannot be PAPP-A2, or any other PAPP.

New claim 96 requires that the fragment be at least 50 a.a. in length. Note that 18 is less than 75% of 50.

5. Double Patenting Issue (OA §27)

The Examiner considers claims 13 and 76 to be substantial duplicates. Claim 13 has been cancelled.

6. Definiteness Issues (OA §§15-21)

The Examiner has raised issues concerning the wording of claims 12 ("fragment thereof"), 13 ("processing variant"), 18 ("recombinant polypeptide") and 77 (reference sequence).

These rejections are moot because claim 12 as amended no longer recites "fragment thereof", while claims 13, 18 and 77 have been cancelled. Fragments are recited in claims 90-96, but

"thereof" is not used. With regard to "processing variants" of claim 96" see, e.g., P43, L25-31 which includes a definition of processing variants, and an example.

7. Description Issues (OA §§22-23)

The Examiner concedes description only for the polypeptide of SEQ ID NO:2, and not for the previously claimed mutants and fragments. The Examiner does not consider this species to be representative of the previously claimed genus.

Claim 12, as examined, recited at least 75% identity. In the Written Description Training Materials, there is an Example in which the single disclosed enzyme is deemed representative of a genus defined by 95% identity. Claim 12, as amended, is even more stringent, as it recites at least 97% identity.

We would also point out that while there are no other specifically disclosed mutants, there are several specifically disclosed fragments, notably 234-1791 (mature PAPP-A2, P43, L33-34), the processing variant 200-1791 (P43, L28-31), and the intercysteine fragments disclosed at P26, L32-P27, L2. All of these can be considered specifically disclosed species, and hence the genus is represented by more than one such species.

8. Enablement Issues (OA §§24-25)

With regard to enablement, the examiner concedes enablement for (1) a polypeptide comprising SEQ ID NO:2, (2) a polypeptide comprising 234-1791 of SEQ ID NO:2, and (3) fragments of SEQ ID NO:2. (OA page 9). However, the Examiner questions enablement for mutants.

Claim 12 now requires that the mutants be at least 97% identical to the recited protein. Given that the PAPP proteins have common activities despite a sequence divergence of around 50%, we believe that the Examiner does not have a reasonable basis to doubt enablement for these very high % identity claimed mutants.

The person skilled in the art is given considerable guidance

as to where PAPP-A2 can and can't be mutated. PP 26-27 imply that knowledge of critical regions on PAPP-A is relevant to design of derivatives of PAPP-A2. The regions most likely to mediate activity are identified by P52, L3-10:

> The sequence motifs of PAPP-A (Kristensen et al., 1994, Biochemistry 33, 1592-8) are also found in PAPP-A2: The catalytic zinc binding motif and residues of the putative Met-turn are underlined and bolded in both sequences. Lin-notch motifs (LNR1-3) and short consensus repeats (SCR-1-5) are boxed. Cysteine residus are shaded. All cysteines of mature PAPP-A are also found in PAPP-A2. In addition, the secreted from of PAPP-A2 has four cysteine residues (Cys-343, Cys-533, Cys-618, and Cys-1268) with no counterpart in PAPP-A.

See also P57, L17-22. As to what mutations might be tolerated, there is a detailed discussion of conservative substitution at P39-40.

Even if some polypeptides meeting just the % identity limitation are inoperative, such inoperative mutants are excluded by the activity limitations. See Ex parte Mark, 12 USPQ2d 1904 (BPAI 1989).

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By: _____
Iver P. Cooper
Reg. No. 28,005

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms
G:\ipc\g-i\hoib\Oxvig1A\pto amendment.wpd